Оригінальні дослідження

Algorithms of diagnosis and therapy of a primary depressive episode

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article;
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Depressive disorders are among the most widespread forms of mental pathology with significant medical and social consequences and require adequate and timely medical assistance. It is known that algorithms are effective methods of optimizing the provision of psychiatric care in order to prevent the development of therapy-resistant forms of mental pathology and reduce their treatment costs, which is particularly relevant in the case of a primary depressive episode (PDE).

The aim of the work is to develop algorithms for rapid diagnosis and therapy of the PDE.

Materials and methods. During 2018–2021, 131 patients (49 men and 82 women) with the PDE who sought outpatient psychiatric help were clinically examined. All subjects were tested to determine the level of depressive disorder, according to the unified clinical protocol of highly specialized medical care, according to the Hamilton Rating Scale for Depression, Hamilton Anxiety Rating Scale, and the Clinical Global Impressions Scale. The clinical-ethological description consisted of three stages: at the first stage, at a patients' first visit, a general description within the framework of a clinical and psychopathological examinations; at the second stage, the clinical-ethological characteristics of non-verbal behavior were studied; at the last, third stage, non-verbal behavior was recoded into ethological elements according to A. A. Korobov's glossary (1991). Statistical analysis was performed using the Statistica 10 license package of application programs.

Results. An algorithm for the PDE diagnosis has been developed based upon four stages: the first one – the symptomatic state diagnosis; the second – clinical-ethological analysis of depressive phenomenon signs and a neurophysiological electroencephalographic (EEG) examination; the third – psycho-experimental examinations using appropriate tools; the fourth – structuring of the obtained diagnostic data, diagnosis verification and development of therapeutic intervention tactics. A therapeutic algorithm for the PDE treatment was also developed and proposed: at the first stage – use of existing antidepressants with proven clinical effectiveness; at the second – switching from a drug in case of its ineffectiveness within 3–4 weeks to another drug with a different mechanism of action; at the third – in case of the previous stage ineffectiveness, using a combination antidepressant therapy (combining drugs of different groups); at the fourth – application of therapeutic schemes using diuretics, pathogenetic psychotherapy and electroconvulsive therapy.

Conclusions. The proposed diagnostic and treatment algorithms are reliable enough to detect and treat such a category as the primary depressive episode. The effectiveness of personalized comprehensive diagnostic and treatment methods for these conditions should be based on the principles of phasing, comprehensiveness, using integrated approaches, combining therapies aimed at developing an adequate attitude to a disease state, mitigating the intensity of negative emotions, restoring internal and external resources of patients.

Алгоритми діагностики та терапії первинного депресивного епізоду

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Депресивні розлади належать до найпоширеніших форм психічної патології з суттєвими медико-соціальними наслідками, потребують адекватної та своєчасної медичної допомоги. Відомо, що саме алгоритми є ефективними методами оптимізації надання психіатричної допомоги для запобігання виникненню резистентних до терапії форм психічної патології та зниження витрат на їх лікування. Це особливо актуально для вперше діагностованих депресивних проявів.

Мета роботи – розроблення алгоритмів швидкої діагностики та терапії первинного депресивного епізоду.

Матеріали та методи. Протягом 2018–2021 рр. клінічно обстежили 131 хворого (49 чоловіків і 82 жінки) з первинним депресивним епізодом, які звернулися за амбулаторною психіатричною допомогою. Всім обстеженим здійснили тестування для визначення рівня депресивного розладу за уніфікованим клінічним протоколом високоспеціалізованої медичної допомоги, за госпітальною шкалою тривоги та депресії Гамільтона, шкалою загального клінічного враження (CGI-S). Клініко-етологічний опис передбачав три етапи: на першому під час первинного звернення здійснювали загальний опис у межах клініко-психопатологічного дослідження; на другому етапі вивчали клініко-етологічні характеристики невербальної поведінки; на третьому здійснювали перекодування невербальної поведінки в етологічні елементи згідно з глосарієм А. А. Коробова (1991). Статистичний аналіз здійснили, застосувавши ліцензійний пакет прикладних програм Statistica 10.

Результати. Розроблено алгоритм діагностики первинного депресивного епізоду, що передбачає чотири етапи: перший – діагностика симптоматичного стану; другий – клініко-етологічний аналіз ознак депресивного феномену та нейрофізіологічне ЕЕГ-обстеження; третій – психоекспериментальне дослідження з використанням відповідного інструментарію; четвертий – структуризація діагностичних даних, верифікація діагнозу та розроблення тактики терапевтичного втручання.

Розробили та запропонували терапевтичний алгоритм лікування первинного депресивного епізоду: на першому етапі – призначення антидепресантів із доведеною клінічною ефективністю; на другому – зміна препарату, якщо він не ефективний протягом 3–4 тижнів, на препарат з іншим механізмом дії; на третьому, – у разі неефективності попереднього етапу, треба

призначати комбіновану терапію антидепресантами (поєднання препаратів різних груп); на четвертому – застосовувати схеми лікування, що включають діуретичні засоби, патогенетичну психотерапію та електросудомну терапію.

Висновки. Запропоновані алгоритми діагностики та лікування доволі надійні під час визначення та терапії пацієнтів із первинним депресивним епізодом. Ефективність методу персоніфікованої комплексної діагностики та терапії цих станів ґрунтується на принципах етапності, комплексності, використанні інтегрованих підходів, поєднанні методів терапії, що спрямована на формування адекватного ставлення до хворобливого стану, пом'якшення інтенсивності негативних емоцій, відновлення внутрішніх і зовнішніх ресурсів пацієнта.

Depressive disorders are among the most widespread forms of mental pathology with significant medical and social consequences that require adequate and timely medical care [1,2,3]. According to modern concepts, prompt diagnosis and prescribing therapy, which should be comprehensive and include pharmaco- and psychotherapy, as well as psychosocial measures, need to begin as early as possible and take into account the main clinical symptoms to avoid the risk of a disease chronic course, reduce the risk of suicide, improve the quality of life and to prevent relapses and exacerbations [4,5,6,7].

It is well known that algorithms are effective methods of optimizing the provision of psychiatric care in order to prevent the development of treatment-resistant depression [8,9,10] and reduce its treatment costs [11]. At the same time, it is necessary to notice that each variant of such an algorithm must be evaluated on the basis of credibility or the level of evidence on its effectiveness, as well as with regard to the risk / effectiveness ratio, that is, not only the proven effectiveness should be considered, but also the frequency and severity of side effects, possible drug interactions and an accordance with general practical expediency.

Diagnostic and treatment errors in the management of depression lead to aggravation of the disease course, increase the risk of suicide, form resistant to therapy conditions and, finally, disability in patients.

Aim

Considering the above, the purpose of this study was to develop algorithms for rapid diagnosis and therapy of a primary depressive episode.

Materials and methods

Following the principles of bioethics, on the basis of informed consent, 131 patients (49 men and 82 women) with the primary depressive episode (PDE), who sought outpatient psychiatric help, were clinically examined in 2018–2021. The mean age of the examined patients at the time of symptom onset was 32.4 ± 3.5 years. The illness duration in patients varied from one to three months (on average 1.9 ± 1.1 months). Diagnostic conclusions were made in accordance with the criteria of ICD-10. At the time of examinations, the patients did not receive drug therapy, had no signs of psychotic disorders and signs of organic damage to the central nervous system. All subjects were tested to determine the level of depressive disorder according to the unified clinical protocol of highly specialized medical care approved by the order of the Ministry of Health of Ukraine dated December 25, 2014 No. 1003, with the Hamilton Rating Scale for Depression (HRSD), Hamilton Anxiety Rating Scale (HARS), and The Clinical Global Impressions Scale (CGI-S).

The clinical-ethological description consisted of three stages using the following methods: at the first stage, at a patients' first visit for medical help, a general description within the framework of a clinical and psychopathological examinations; at the second stage, the clinical and ethological characteristics of non-verbal behavior (NB) were studied; at the last, third stage, NB was recoded into ethological elements according to A. A. Korobov's glossary (1991).

Subsequently, after the completion of examinations and procedures for formulating a clinical diagnosis according to ICD-10, the distribution of patients into groups of endogenous and psychogenic origin was carried out, and the results were processed.

Electroencephalography (EEG) was recorded on a 16-channel computer electroencephalograph "Neurokom 19"; 16 monopolar leads were used. The recording was conducted in a state of rest with closed eyes. The average duration of observation was 20 minutes. After removing the artifacts using a specified diagnostic complex software, spectral analysis of EEG signals and estimation of the average EEG amplitude for each lead was done.

Statistical analysis was performed using the Statistica 10 license package of application programs.

Results

At the initial stage of the examination, the symptomatic condition was diagnosed. For this, we used a generally accepted clinical-phenomenological method that allowed us to find out the main directions of conducting psychophenomenological diagnostics and to form a picture reflecting the pathodynamic aspect of the disease activity, the phase of its development, the nature and expressiveness of the basic disintegration, the presence of disontogenesis signs, in the light of the study on social aspects of functional diagnosis. It helped to reveal external conditions of maladaptation caused by the meaningful environment influence (family, professional environments, microsocial groups, social institutions) – somato-biological prerequisites for the formation of compensatory and adaptive process violations.

At the second stage of the diagnostic process, clinical and ethological analyses of the depressive phenomenon signs and neurophysiological EEG examinations of the neural activity parameters in PDE were carried out followed by the formation of a preliminary identification of its etiological aspect.

The third stage of the diagnostic process was based on the application of a psycho-experimental analysis using the HRSD, HARS, CGI-S and aimed at confirming the data of the clinical-phenomenological approach to make a diagnosis and determining the degree of PDE course severity at the time of the examination for modeling further therapeutic strategies.
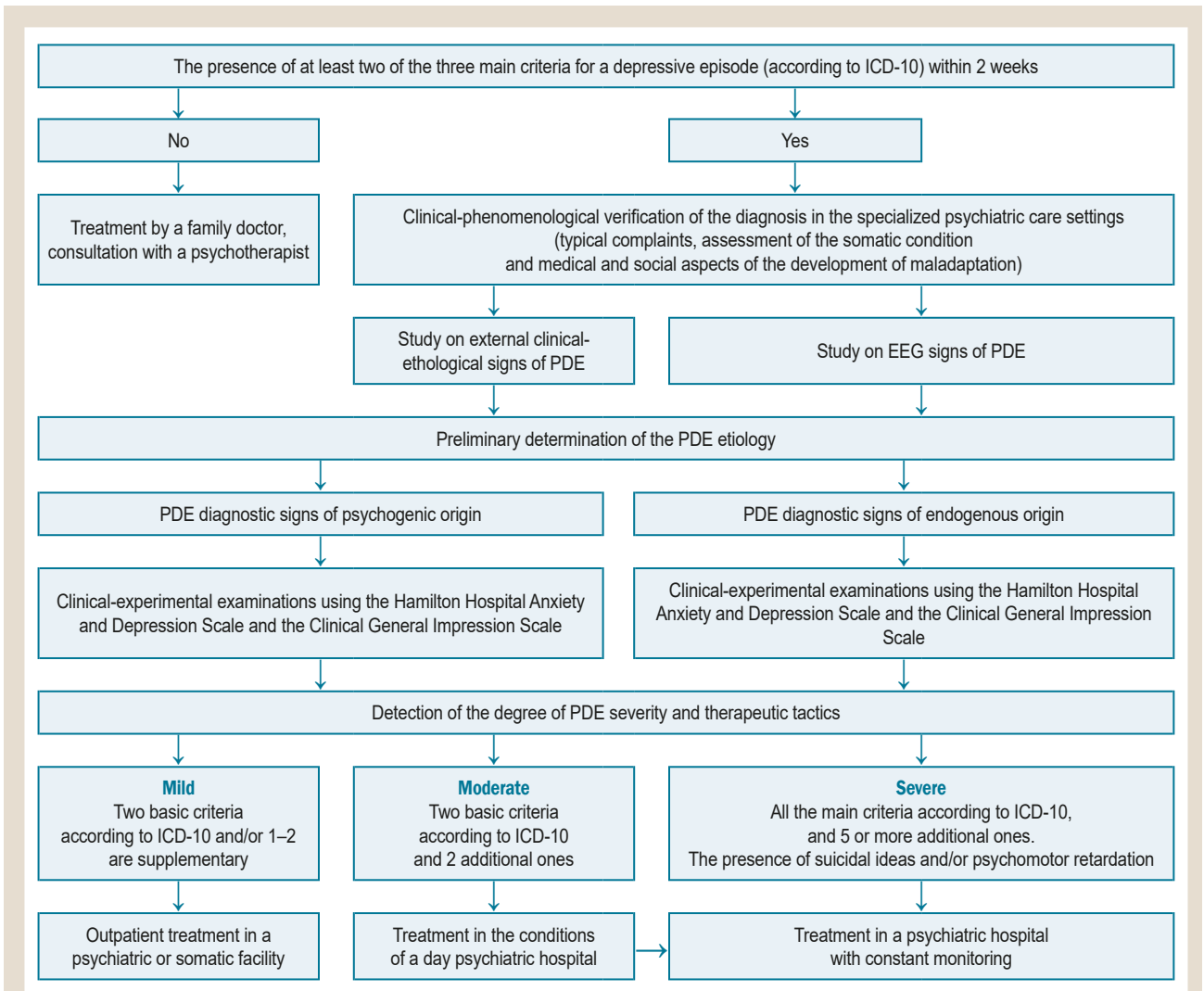
Fig. 1. Algorithm for diagnosis of a primary depressive episode.

At the fourth stage, the obtained diagnostic data structuring, verification of the diagnosis and the development of therapeutic intervention tactics were carried out (*Fig. 1*).

The diagnosis and initial evaluation of the depressive syndrome, which also included a thorough somatic examination of patients, were conducted in the conditions of a specialized psychiatric care facility. At the final stage of the diagnostic algorithm, before the start of the therapy, an individual treatment plan was drawn up taking into account the sequence of different stages of therapy, clinical features of the condition, the severity of manifestations and the risk of suicide, patient compliance, the presence of concomitant diseases and related therapies.

Treatment for mild PDE should usually be done on an outpatient basis within the primary psychiatric or physical care settings. Depending on the individual characteristics and/or requests of patients, a prescription of antidepressants was quite effective. In some cases, PDE of psychogenic origin could be confined to the use of psychotherapeutic, psychoeducational or social rehabilitation methods.

Treatment of patients with moderate PDE, depending on the characteristics and social conditions, was usually carried out in a day hospital or, in case of rapid deterioration, in a psychiatric hospital. When choosing treatment tactics, it was mandatory to consider social factors, such as a high risk of sudden changes in the status of patients living alone, as well as a possible rising of suicidal ideation, the treatment for such patients was preferable to apply in hospital settings.

Treatment of patients with severe PDE was carried out exclusively in inpatient department settings, sometimes, even without a consent of patients with suicidal ideation, in accordance with the current legislation by a court decision. Patients with a high suicidal risk required particularly careful management and special psychological correction. In the case of suicidal intent that persisted for a long time and not amenable to medical correction, it was necessary to consider the possibility of rapid electroconvulsive therapy (ECT).

Based on the results of our study, the use of the proposed diagnostic algorithm has allowed to optimize the psychiatric examination in case of suspected PDE in comparison with the classical clinical-phenomenological approach which only assesses the mental state detecting
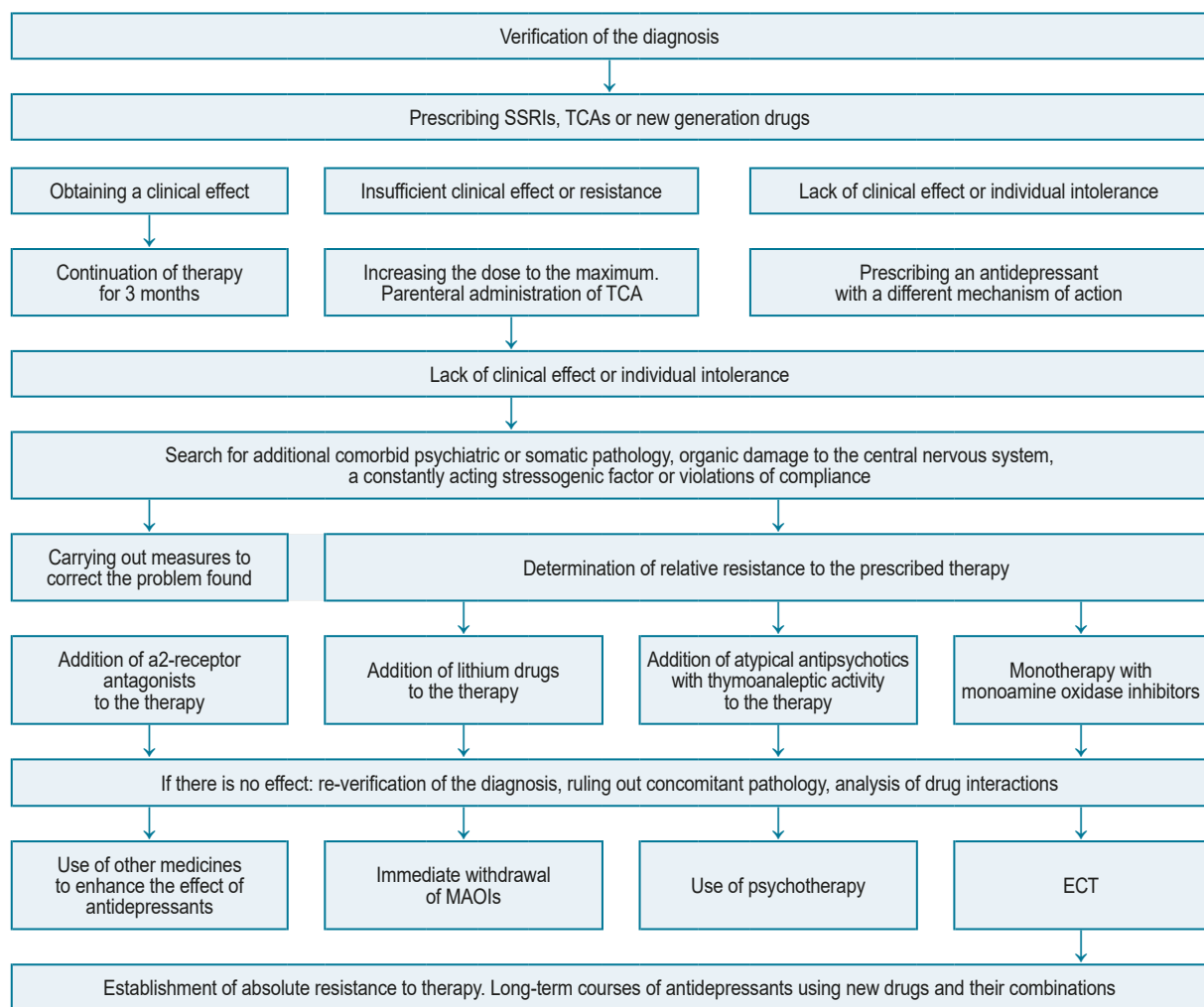
Fig. 2. Algorithm for the treatment of a primary depressive episode.

signs sufficient for the developed syndrome diagnosis. Our proposed multi-level diagnostic algorithm has increased the accuracy of diagnosis by 36.4 % and has led to the assumption about the causes of the disorder, assessment of the condition severity level at the time of examinations considering external and neurophysiological signs and prediction of potential directions for therapy and psychoprophylaxis.

The treatment results of patients with the diagnosis of PDE were catamnestically evaluated over the course of a year, enabling us to develop and propose the therapeutic algorithm for the treatment of PDE (*Fig. 2*) without psychotic symptoms and syndromic features of depression. It involved the consistent implementation of the following strategies.

At the first stage, we used existing antidepressants with proven clinical efficacy to initiate PDE therapy. However, for the treatment of severe depression, it was advisable to immediately choose a drug with a wide spectrum of neurochemical mechanism of action (SNRIs, TCAs). For the treatment of moderately expressed depression, preference was given to SSRIs and other new generation antidepressants. If there was an effect within 3–4 weeks, the therapy was continued until reaching a remission. In the absence of dynamics or insufficient effect (the degree of symptom reduction of less than 50 %), patients were switched to the second course or stage of therapy: drug changes or dose escalation to the maximum in cases of suspected resistance, or partial administration of parenteral TCA. An ineffective antidepressant was usually replaced by a drug with a different action mechanism.

According to some literary sources [12], a small but statistically significant advantage of using a drug replacement with a different mechanism of action has been shown. There is no more convincing evidence of such replacement effectiveness compared with switching to another drug from the same group.

Nevertheless, current definitions of therapeutic-resistant depression assume the ineffectiveness (i. e., the reduction of symptoms according to the Hamilton scale of no more than 50 %) of two consecutive courses of adequate monotherapy lasting an average of 3–4 weeks with pharmacologically different antidepressants in terms of structure and neurochemical action [13,14,15].

In case of insufficient clinical effect and the absence of defined reasons for such ineffectiveness, including erroneous or incomplete diagnosis, non-compliance, comorbid mental and somatic diseases and other factors, it was necessary to treat this situation as a relative resistance and proceed to the third stage including:

– therapy with a combination of antidepressants;

– combination antidepressant therapy with lithium or triiodothyronine;

– combination therapy of antidepressants and antipsychotics with a thymoanaleptic effect;

– a course of MAOI monotherapy.

At the same time, depending on the situation, any option of therapy with a course duration of 3–4 weeks could be chosen, but preference was given to agents with proven effectiveness, good tolerability and possible drug interactions, including those resulting from competitive hepatic metabolism, that was also considered. The negative aspects of such a strategy included an increased risk of drug interactions, side effects, and higher costs.

In the case of the mentioned measures ineffectiveness, there was a transition to the fourth stage, which also included several options:

– application of unused combinations of the third stage;

– immediate withdrawal of the therapy with the use of diuretics;

– addition of pathogenetic psychotherapy (cognitive-behavior therapy (CBT), suggestion, etc.);

– standardized course of ECT procedures.

The main point of this stage and the most powerful method of overcoming therapeutic resistance was a course of ECT in the form of monotherapy or alongside antidepressants use. The effectiveness of a 6-session course of ECT (2 weeks, 3 sessions per week every other day) was 68 % and exceeded the effectiveness of all other options for overcoming resistance in our study on the example of 11 patients.

Therefore, in our opinion, preference should be given to ECT over other methods of this stage in the absence of contraindications in order to counteract the further chronicity of depression.

In case of ineffectiveness of all the planned stages, and especially the course of ECT, absolute resistance should have been considered proceeding to the fifth stage consisting in long-term courses of previously not used antidepressants, new options for combined therapy, including the combination of presynaptic reuptake inhibitors with MAOIs. Upon reaching the effect of overcoming resistance, it was necessary to continue the selected therapy for at least 6 months in order to ensure a complete reduction of residual symptoms and achieve a stable remission [16,17].

During the study result analysis, the most common diagnostic and medication errors in PDE have been identified:

– incorrect interpretation of mood disorder symptoms as a diagnosis of PDE;

– prescription of antidepressants with stimulant effect as the first course of therapy for PDE with anxiety syndrome;

– prescription of sedative antidepressants as the first course of therapy for PDE with the presence of psychomotor retardation;

– inadequate duration of antidepressant treatment courses;

– use of antidepressants at low or medium therapeutic doses;

– untimely detection and/or lack of adequate therapy for comorbid mental and somatic disorders;

– early withdrawal of effective therapy by a doctor or patient due to insufficient compliance.

Discussion

It should be noted that the obtained results do not contradict the conclusions of previous studies by national and foreign scientists and once again confirm that the use of PDE diagnostic algorithms are quite reliable in identifying and treating such a category as "depressive episode" [1,3,7]. The step-by-step approach in the management of PDE with a continuous assessment of its therapeutic resistance degree is the most effective, which has been repeatedly proven [2,13,15].

Using this approach formalizes the process of patient management and makes therapy more available. The PDE algorithm proposed in the framework of our study corresponds to the current criteria of modern diagnostic and therapeutic tools [16,17].

Prospects for further research are to create an integrative system for diagnosis and treatment of PDE using data from neurophysiological, clinical, ethological and experimental-psychological components.

Conclusions

1. The proposed diagnostic and treatment algorithms are reliable enough to detect and treat such a category as the primary depressive episode.

2. The effectiveness of personalized comprehensive diagnostic and treatment methods for these conditions should be based on the principles of phasing, comprehensiveness, using integrated approaches, combining therapies aimed at developing an adequate attitude to a disease state, mitigating the intensity of negative emotions, restoring internal and external resources of patients.

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References

1. Adli, M., Rush, A. J., Möller, H. J., & Bauer, M. (2003). Algorithms for optimizing the treatment of depression: making the right decision at the right time. *Pharmacopsychiatry*, *36*(Suppl 3), S222-S229. https://doi.org/10.1055/s-2003-45134

2. Mann, J. J. (2005). The medical management of depression. The *New England journal of medicine*, *353*(17), 1819-1834. https://doi.org/10.1056/NEJMra050730

3. Bauer, M., Pfennig, A., Linden, M., Smolka, M. N., Neu, P., & Adli, M. (2009). Efficacy of an algorithm-guided treatment compared with treatment as usual: a randomized, controlled study of inpatients with depression. *Journal of clinical psychopharmacology*, *29*(4), 327-333. https://doi.org/10.1097/JCP.0b013e3181ac4839

4. Ricken, R., Wiethoff, K., Reinhold, T., Schietsch, K., Stamm, T., Kiermeir, J., Neu, P., Heinz, A., Bauer, M., & Adli, M. (2011). Algorithm-guided treatment of depression reduces treatment costs--results from the randomized controlled German Algorithm Project (GAPII). *Journal of affective disorders*, *134*(1-3), 249-256. https://doi.org/10.1016/j.jad.2011.05.053

5. Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., & Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *The American journal of psychiatry, 163*(11), 1905-1917. https://doi.org/10.1176/ajp.2006.163.11.1905

6. Richardson, K., & Barkham, M. (2020). Recovery from depression: a systematic review of perceptions and associated factors. *Journal of mental health*, *29*(1), 103-115. https://doi.org/10.1080/09638237.2017.1370629

7. Maruta, N. O., & Zhupanova, D. O. (2016). Kliniko-psykholohichni osoblyvosti khvorykh na depresiiu z riznym rivnem medykamentoznoho komplaiensu (diahnostyka i korektsiia) [Clinical-psychological peculiarities of patients with depression and different levels of medication compliance (diagnosis and correction)]. *Ukrainskyi visnyk psykhonevrolohii*, *24*(1), 5-11. [in Ukrainian].

8. Bennabi, D., Aouizerate, B., El-Hage, W., Doumy, O., Moliere, F., Courtet, P., Nieto, I., Bellivier, F., Bubrovsky, M., Vaiva, G., Holztmann, J., Bougerol, T., Richieri, R., Lancon, C., Camus, V., Saba, G., Haesbaert, F., d'Amato, T., Charpeaud, T., Llorca, P. M., … Haffen, E. (2015). Risk factors for treatment resistance in unipolar depression: a systematic review. *Journal of affective disorders, 171*, 137-141. https://doi.org/10.1016/j.jad.2014.09.020

9. Lamers, F., de Jonge, P., Nolen, W. A., Smit, J. H., Zitman, F. G., Beekman, A. T., & Penninx, B. W. (2010). Identifying depressive subtypes in a large cohort study: results from the Netherlands Study of Depression and Anxiety (NESDA). *The Journal of clinical psychiatry*, *71*(12), 1582-1589. https://doi.org/10.4088/JCP.09m05398blu

10. Troyan, O. S., Levada, O. A. (2021). Ageadjusted normative data and discriminative validity of cognitive tests in the Ukrainian adult patients with major depressive disorder. *Modern Medical Technology*, (2), 4-14. https://doi.org/10.34287/MMT.2(49).2021.1

11. Maruta, N. A., Yavdak, Y. A., & Cheredniakova, E. S. (2017). Otsenka neirotroficheskoi terapii depressii [Evaluation the neurotrophic therapy of depression]. *Mizhnarodnyi nevrolohichnyi zhurnal*, (3), 29-38. [in Russsian]. https://doi.org/10.22141/2224-0713.3.89.2017.104240

12. Papakostas, G. I., Fava, M., & Thase, M. E. (2008). Treatment of SSRI-Resistant Depression: A Meta-Analysis Comparing Within- Versus Across-Class Switches. *Biological Psychiatry*, *63*(7), 699-704. https://doi.org/10.1016/j.biopsych.2007.08.010

13. Ricken, R., Wiethoff, K., Reinhold, T., Schietsch, K., Stamm, T., Kiermeir, J., Neu, P., Heinz, A., Bauer, M., & Adli, M. (2011). Algorithm-guided treatment of depression reduces treatment costs--results from the randomized controlled German Algorithm Project (GAPII). *Journal of affective disorders*, *134*(1-3), 249-256. https://doi.org/10.1016/j.jad.2011.05.053

14. Trivedi, M. H., Fava, M., Wisniewski, S. R., Thase, M. E., Quitkin, F., Warden, D., Ritz, L., Nierenberg, A. A., Lebowitz, B. D., Biggs, M. M., Luther, J. F., Shores-Wilson, K., Rush, A. J., & STAR*D Study Team (2006). Medication augmentation after the failure of SSRIs for depression. *The New England journal of medicine*, *354*(12), 1243-1252. https://doi.org/10.1056/NEJMoa052964

15. Davies, P., Ijaz, S., Williams, C. J., Kessler, D., Lewis, G., & Wiles, N. (2019). Pharmacological interventions for treatment-resistant depression in adults. *The Cochrane database of systematic reviews*, *12*(12), CD010557. https://doi.org/10.1002/14651858.CD010557.pub2

16. Kupfer, D. J. (1993). Management of recurrent depression. *The Journal of Clinical Psychiatry*, *54*(2, Suppl), 29-33.

17. Rush, A. J., & Kupfer, D. J. (2001). Strategies and tactics in the treatment of depression. In G. O. Gabbard (Ed.), *Treatment of Psychiatric Disorders* (p. 1417-1439). American Psychiatric Publishing, Inc.

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